Guidance for Industry

Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance document are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm

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U.S. Department of Health and Human Services
Food and Drug Administration
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GUIDANCE FOR INDUSTRY[1]

Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture

I. INTRODUCTION

Frequently, a licensed manufacturer determines that it is appropriate to make a change in the product, labeling, production process, quality controls, equipment, or facilities as documented in it's approved license application(s). Section 601.12 of Title 21, Code of Federal Regulations (21 CFR 601.12) prescribes the requirements for reporting such changes for licensed biological products to the Food and Drug Administration (FDA).

Under 21 CFR 601.12, a change to an approved product, labeling, production process, quality controls, equipment, or facilities is required to be reported to FDA in: 1) a supplement requiring approval prior to distribution; 2) a supplement submitted at least 30 days prior to distribution of the product made using the change; or 3) an annual report, depending on its potential to have an adverse effect on the "identity, strength, quality, purity, or potency of the biological product as they may relate to the safety or effectiveness of the product" (1) (hereinafter referred to in this document as "the safety or effectiveness of the product"). Before distributing a licensed product manufactured using a change, applicants are required to demonstrate, through appropriate validation and/or clinical or non-clinical laboratory studies, the lack of adverse effect of the change on the safety or effectiveness of the product.

The three reporting categories for changes to an approved application are defined in 21 CFR 601.12:

1) Changes that have a substantial potential to have an adverse effect on the safety or effectiveness of the product, which require submission of a supplement and approval by FDA prior to distribution of the product made using the change (major changes);

[1] This guidance document represents FDA's current thinking on changes to an approved application for all licensed human blood and blood components intended for transfusion or for further manufacture. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

2) Changes that have a moderate potential to have an adverse effect on the safety or effectiveness of the product, which require submission of a supplement to FDA at least 30 days prior to distribution of the product made using the change (moderate changes); and

3) Changes that have minimal potential to have an adverse effect on the safety or effectiveness of the product, which are to be described by the applicant in an annual report (minor changes).

In response to the comments received after the publication of the July 1997, Guidance for Industry - Changes to an Approved Application: Biological Products (2), and the Biologics Workshop presented by the Center for Biologics Evaluation and Research (CBER) on December 2, 1997, regarding the Biologics License Application (BLA) and the reporting requirements for changes to an approved application (3), CBER has developed this additional, more specific guidance for the manufacturers of licensed Whole Blood and blood components intended for transfusion and for further manufacture into both injectable and non-injectable products. This guidance applies to the manufacture of all licensed Whole Blood, blood components, Source Plasma, and Source Leukocytes. This guidance is intended to assist manufacturers in determining which reporting mechanism is appropriate for a change to an approved license application and when final, will replace the recommendations in the Guidance for Industry: Changes to an Approved Application: Biological Products, July 1997, for the above mentioned products.

In addition to the requirements contained in 21 CFR 601.12, an applicant making a change to an approved license application must conform to other applicable laws and regulations, including the current good manufacturing practice (cGMP) requirements of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(B)) and regulations in 21 CFR parts 210, 211, and 600 through 680. For example, manufacturers must comply with recordkeeping requirements and ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection.

Under each section of this guidance document, FDA provides categories of changes to be reported under 21 CFR 601.12. A listing of various changes that FDA currently believes fall under each category is also provided. The lists are not intended to be all-inclusive. Some of the changes listed in a specific reporting category in the July 1997 guidance document on reporting changes to an approved application for biological products have been moved to other reporting categories in this guidance document. In addition, this guidance describes the format for the annual report and further explains the comparability protocol. A separate section on labeling describes those labeling changes to be submitted as supplements requiring prior approval, supplements submitted at the time the change is made or included in the annual report. Applicants requiring further guidance are encouraged to call the Division of Blood Applications.

Because the individual establishment and product licenses are being replaced by a single biologics license (4), applicants now have the option to combine or bundle multiple changes into one submission, e.g., report a change in the manufacture of one or more product(s) at one or more manufacturing location(s). For clarity, FDA requests that bundling be limited to related changes. If the review of a bundled submission cannot be completed, CBER will separate the supplements still under review from the supplements for which the review is complete and final action (e.g., approval) can go forward. CBER has published additional guidance describing the specific items that are to be included in a submission (5).

Applicants should prominently label each submission with the reporting category under which the change is being reported, e.g., "Prior Approval Supplement", "Supplement - Changes Being Effected in 30 Days", "Supplement - Changes Being Effected" or "Annual Report." Each submission should include a Form FDA 356h "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use" (6). FDA continues to encourage applicants to use a cover letter to introduce and summarize the supplement. For guidance in preparing a supplement, applicants may refer to the Guidance for Industry – For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the Form FDA 356h "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use" (5).

Manufacturers should report changes to their approved establishment, product or biologics license applications to the Director, Center for Biologics Evaluation and Research, Office of Blood Research and Review, Division of Blood Applications, HFM-370, c/o Document Control Center (HFM-99), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448.

II. DEFINITIONS

Acquisition - the purchase of a facility previously operated by an applicant under one U.S. license number by an applicant holding a different U.S. license number or by a new applicant. The acquired facility will no longer be connected to the original U.S. license number. The original license will either be revoked or modified to delete the facility. The license application for the legal entity acquiring the facility will be supplemented to include the manufacture of product at the acquired facility. If a new applicant has acquired a facility, a new license will be granted. Acquisitions were previously referred to as 'rollovers' (7).

Applicant - any person or legal entity that has submitted an application to manufacture a product subject to licensure under section 351 of the Public Health Service Act (PHS Act). The applicant assumes responsibility for compliance with the applicable product and establishment standards and for Quality Assurance (QA) oversight of all manufacturing steps (8). Also see **manufacturer.**

Application - request submitted by the applicant for a biologics license, including supportive documentation, in order to manufacture a product subject to licensure under section 351 of the PHS Act.

Authorized Official - person(s) designated by the applicant to communicate with the FDA on behalf of the applicant. Authorized officials can initiate applications or supplements to a license application, discuss submissions with FDA representatives, provide additional information in support of the submissions, and withdraw applications or supplements (9). The manufacturer or applicant should immediately notify CBER in writing if there is a change in the authorized official(s). CBER will acknowledge receipt of the notification.

Circular of Information - instruction circular that provides adequate directions for the use of blood products intended for transfusion. The circular contains descriptions of the blood products, information on the tests performed on the components, indications for use, contraindications, cautions and administration recommendations [21 CFR 606.122].

Contractor - any person or entity, other than the applicant, that performs part or all of the manufacturing of the licensed product as a service to the applicant. The applicant assumes responsibility for the contractor's compliance with the applicable product and establishment standards. Both the applicant and contractor will be held legally responsible for the work performed by the contractor. All contractors performing a manufacturing step of a licensed product must be registered with FDA, unless they are exempt from registration [21 CFR part 607] (10).

Contractual Agreement –agreement between a manufacturer and a contractor, which describes the manufacturing steps performed by the contractor. The specific legal contract need not be included in the submission, but the applicant should include a description of the services requested from all contractors performing a manufacturing step for the manufacturer (e.g., outside testing laboratories performing routine donor/product testing and confirmatory testing, irradiation facilities, suppliers of Red Blood Cells for immunization, storage facilities). This should also be available on site for review during inspection.

Disease Associated Antibody Donors - donors who meet all the required/recommended normal Source Plasma donor suitability criteria, but whose plasma contains pre-existing IgG antibodies as a result of previous exposure to certain diseases or cellular antigens (11).

Disease State/High Risk Donors - donors whose plasma contains or lacks a specific property (e.g., protein, antibody, inherited trait) as a result of their disease. These donors may not meet all the required or recommended normal Source Plasma donor suitability criteria.

Establishment/Facility - includes any and all facilities used by the manufacturer for collection, processing, product testing, compatibility testing, storage, or distribution of blood components. Any facility in which a manufacturing step is performed must meet the specifications and

procedures established in the biologics license application designed to insure the continued safety, purity and potency of the biological product [21 CFR 600.3(w)]. Establishment and facility have the same meaning (4). For the purposes of this document, facilities will be separated into three categories determined by the manufacturing steps they perform: Major Facilities, Auxiliary Facilities and Transfusion Services (see Appendix D).

Major Facilities:

- **Collection Facility -** facility that collects Whole Blood, apheresis products, and/or infrequent plasmapheresis but which does not perform FDA required or recommended blood and plasma donor testing or prepare components from Whole Blood. Collection facilities may also label, store and distribute blood products.

- **Community Blood Bank -** commercial or non-profit blood collection/processing facility, not part of a hospital system, which may perform manual and/or automated blood collection, prepare components from Whole Blood, perform FDA required or recommended blood and plasma donor testing (including compatibility testing), and routinely label, store and distribute blood and/or blood products to one or more hospitals. Community blood banks may also prepare irradiated, frozen, deglycerolized and/or leukoreduced products.

- **Component Preparation Facility -** intermediate processing facility which prepares components from Whole Blood collected at a mobile or fixed collection site but does not perform FDA required or recommended blood and plasma donor testing. Component preparation facilities may also perform automated collection of blood products, and/or label, store and distribute blood products and/or may prepare irradiated, frozen, deglycerolized and/or leukoreduced products.

- **Hospital Blood Bank -** facility located within a hospital which routinely performs manual and/or automated blood collection and processes Whole Blood into components. A hospital blood bank may also prepare irradiated, frozen, deglycerolized and/or leukoreduced products, distribute blood products to other hospitals and may perform FDA required or recommended blood and plasma donor testing and compatibility testing.

- **Plasmapheresis Center -** facility licensed by CBER which collects Source Plasma by manual and/or automated methods for commercial distribution. Plasmapheresis centers may also perform FDA required or recommended blood and plasma donor testing.

- **Product Testing Laboratory –** facility that performs routine FDA required or recommended blood and plasma donor testing.

Auxiliary Facilities:

- **Distribution Center -** facility that stores blood or a blood product under specific controlled conditions prior to shipment to the final user, including suppliers of source material for further manufacture, such as Recovered Plasma, Source Plasma, Whole Blood, Red Blood Cells, or Platelets for diagnostic product use; for example, Whole Blood facilities which intend to redistribute the product to transfusion centers, Source Plasma warehouses which intend to redistribute the product to fractionators or Recovered Plasma holding facilities or brokers intending to redistribute the product to diagnostic product manufacturers or fractionators.

- **Donor Center -** facility that only performs manual collection of Whole Blood and does not collect blood product by automated methods, prepare blood components or perform routine FDA required or recommended blood and plasma donor testing.

Transfusion Services:

- **Hospital Transfusion Service -** hospital that performs compatibility testing for blood and blood components, but does not routinely collect blood, process Whole Blood into components (except Red Blood Cells and Recovered Plasma) and does not perform FDA required or recommended blood and plasma donor testing.

Fractionated Blood Derivatives - sterile solutions of a specific protein(s) derived from human blood, e.g., albumin, plasma protein fraction and immune globulin.

Manufacturer - any person or legal entity engaged in the manufacture of a product subject to licensure under the PHS Act. Manufacturer also includes any person or legal entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards [21 CFR 600.3(t)].

Manufacturing - all steps involved in the preparation of a product intended for transfusion or for further manufacture into injectable or non-injectable products. Manufacturing includes determining donor suitability, the informed consent and collection procedure, component preparation, product/donor testing (including quality control), labeling, storage of the product, compatibility testing, and the quarantine and destruction of unsuitable blood products [21 CFR 600.3(u) and 21 CFR 607.3(d)]. The steps may be performed by the manufacturer holding the biologics license or by a contractor who performs one or more of the manufacturing steps.

Merger - union of two or more licensed manufacturers to form a new legal entity. A new U.S. license number will be issued to the new entity.

Source Material - blood component derived from human blood that is collected by either manual or automated apheresis techniques and is intended for further manufacturing into injectable or non-injectable products.

Supplement - written request submitted to the Director, Center for Biologics Evaluation and Research, to approve a change in an approved license application [21 CFR 600.3(gg)].

Transfusion Blood Components - blood components (Whole Blood, Red Blood Cells, Platelets, Plasma, Cryoprecipitate, or Leukocytes) derived from human blood collected by either manual whole blood collection or automated apheresis techniques and intended to be transfused to human recipients.

III. CHANGES UNDER 21 CFR 601.12(b) - Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes). [PAS]

Under 21 CFR 601.12(b), any change to a product, production process, quality controls, facilities, or equipment, that has a substantial potential to have an adverse effect on the safety or effectiveness of the product, require submission of a supplement and approval by FDA before a product made using the change is distributed. For a change under this category, an applicant is required to submit a supplement to the approved license application that includes the following: a detailed description of the proposed change; the products involved; the manufacturing site(s) or area(s) affected; a description of the methods used and studies performed to evaluate the effect of the change on the product's safety or effectiveness; the data derived from those studies; relevant validation protocols and data; appropriate labels; and relevant standard operating procedure(s) (SOP) or a list referencing previously approved relevant SOP. As noted, the applicant must obtain approval of the supplement by FDA prior to distribution of the product made using the change.

Any change in a facility or manufacturing process should be submitted in the prior approval category unless specified in this guidance that it may be reported in another category. FDA considers the following types of changes to be major changes, for which submission and approval of a supplement prior to distribution of product made using the change should occur:

A. Product Manufacturing/Procedural Changes

1. Implementation of a new manufacturing process, to include but not be limited to:
    a. Leukocyte reduction
    b. Irradiation
    c. Freezing/deglycerolizing
    d. Rejuvenating
    e. Washing

2. Addition or revision of SOP for the following categories if the change is less restrictive than previously approved or is not addressed in published FDA guidance documents* (7):
    a. Donor suitability, including donor deferral
    b. Blood collection, including arm preparation
    c. High risk behavior questions, including AIDS information
    d. Donor history forms, including informed consent
    e. Product manufacturing for licensed products
    f. Quarantine and disposition of unsuitable product

    ***NOTES**:
    - Changes in format only and minor editorial changes to SOP and forms do not need to be reported. Report only changes in the content of the procedure or form.
    - The manufacturer may reference previously approved SOP and forms. The FDA application or supplement tracking number should be included when referencing a previously approved SOP or form.
    - SOP revisions in the above areas prepared in response to post-approval FDA inspections should be submitted to FDA for review. SOP revisions prepared in response to pre-license or pre-approval FDA inspections should be submitted to FDA as amendments to the application or supplement under review.
3. Addition of procedures and/or donor history forms that deviate from the FDA-approved Uniform Donor History Questionnaire, manufacturer's directions or recommendations described in FDA guidance documents. This includes change in quality control procedures. If the modifications are more restrictive or if the procedure is performed following the manufacturer's directions, the change may be reported as a CBE30 or in the annual report (see sections IV.A.1. and VI.A.). Addition of procedures or tests that are not required or recommended by FDA may be reported in the annual report.
4. Change from manufacturing a sole product by automated apheresis to manufacturing additional product(s) as a by-product. Exception: Collection of plasma as a by-product to an approved plateletpheresis program should be reported as a CBE30 (see section IV.A.2.).
5. Request to manufacture additional products; e.g., Plasma Cryoprecipitate-Reduced, Fresh Frozen Plasma Donor Retested.
6. Addition of an immunization program for Red Blood Cells or unlicensed vaccines.
7. Implementation of a physician substitute program in a Source Plasma facility (12).
8. Collection of Source Plasma from disease state or high-risk donors.
9. Request for approval of a comparability protocol.
10. Request for approval of an alternative procedure under 21 CFR 640.120 for which there is no published guidance, e.g., computer/electronic crossmatch.

B. Equipment Changes

1. Conversion from manual to automated collection of blood components; e.g., Platelets, Plasma (both Fresh Frozen and Source), Red Blood Cells, Leukocytes.
2. Changes or upgrades in automated apheresis equipment that affects the purity, potency or quality of the product(s). These changes include but are not limited to: decrease in donation time, increase in product yield, change in storage conditions, change in anticoagulant, leukoreduction, collection of an additional or different product); for example, a change from COBE LRS Version 5.1 to Turbo Version 7.

C. Contractor Changes

1. Change to a new facility or any facility not previously engaged in blood product testing as a contract testing laboratory to perform the routine serologic and infectious disease screening testing, and supplemental and/or confirmatory testing for blood and blood products (test of record).
2. Use of or change in a contractor to perform a manufacturing step, to include but not be limited to: irradiation of blood products, supplier of Red Blood Cells for immunization, provider of personnel responsible for collecting blood products.

D. Facility Changes

1. Expanding operations by the addition of a major facility where licensed products are manufactured. This includes the addition of a contractor to perform the manufacturing step.
    a. Major facilities where Red Blood Cells, Fresh Frozen Plasma, Platelets, and Platelets, Pheresis are collected using automated collection systems, Source Plasma and Source Leukocytes are collected using either manual or automated collection methods, and routine FDA required or recommended blood and plasma testing is performed.
    b. Acquisition of major facilities previously operating under another U.S. license number that will now manufacture product under the U.S. license number of the legal entity acquiring the facility.
2. Relocation of a major facility where product manufacturing is performed that results in a change in center personnel, and/or a change in SOP or equipment. The applicant should also report the relocation of any contractor that results in a change in personnel and/or a change in SOP or equipment.

IV. CHANGES UNDER 21 CFR 601.12(c) - Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change (moderate changes). [CBE30]

Under 21 CFR 601.12(c), changes to a product, production process, quality controls, equipment, or facilities that have a moderate potential to have an adverse effect on the safety or effectiveness of the product require submission of a supplement to FDA at least 30 days prior to distribution of a licensed product made using the change. The requirements for the content of these supplements are the same as for those requiring approval prior to distribution.

The applicant shall specify that the changes are being reported in this category by labeling the submission: "Supplement - Changes Being Effected in 30 Days." Within 30 days of the date FDA receives the submission, CBER will determine if the change or changes have been reported in the proper category and will notify the applicant if they have not. If CBER has not notified the applicant otherwise within 30 days of the receipt of the supplement, the applicant may distribute under licensure, the product made using the change described in the supplement. Lack of notification from FDA does not constitute CBER approval of the changes reported in the supplement, merely that the changes were reported in the proper category. CBER review of the submission will proceed after it has been determined that the changes have been reported in the proper category. There may be instances where FDA determines that the information submitted in the supplement fails to adequately demonstrate the continued safety or effectiveness of the product made using the change. In such cases, FDA will make all possible efforts to resolve the problems with the applicant concerning the supplement submission. In assessing an applicant's plans to correct the problem, the agency intends to consider the applicant's reasons for making the change and the available alternative to the change. In cases where FDA determines that there may be a danger to public health due to the continued marketing of the product, or when FDA determines that the issues may not otherwise be resolved, the agency may require under this section that the applicant cease distribution of the product made using the change or that the product be removed from distribution pending resolution of the issues related to the change.

The applicant will not be notified of the date these supplements are received; instead, FDA recommends that the applicant have a mechanism to track the date FDA received the submission; e.g., a mail service that will return confirmation of the receipt date.

FDA considers the following types of changes to be moderate changes, for which submission of a supplement at least 30 days prior to the distribution of product made using the change should occur:

A. Product Manufacturing/Procedural Changes

1. Revision of SOP for the following categories if the change is more restrictive than previously approved and is not addressed in published FDA guidance documents:
    a. Donor suitability, including donor deferral
    b. Blood collection, including arm preparation
    c. High risk behavior questions, including AIDS information
    d. Donor history forms, including informed consent
    e. Product manufacturing for licensed products
    f. Quarantine and disposition of unsuitable product
2. Addition of the collection of plasma as a by-product in an approved plateletpheresis program, provided the applicant is otherwise approved to manufacture the plasma product.
3. Implementation of an immunization program for licensed vaccines where the program is consistent with the vaccine insert instructions.
4. Request for an alternative procedure under 21 CFR 640.120 for which published guidance is available and implementation conforms with the criteria described in the guidance, e.g., implementation of an infrequent plasmapheresis donor collection program.

B. Equipment Changes

1. Change in manufacturer of automated plasma apheresis equipment, e.g., change from Haemonetics PCS to Fenwal Autopheresis C.

C. Contractor Changes

1. Change to an FDA registered contract testing laboratory, currently engaged in blood product testing, to perform the routine serologic and infectious disease screening testing, and supplemental and/or confirmatory testing for blood and blood products (tests of record).
2. Use of an off-site contract storage facility to store unlicensed product collected under a pending license application or for the storage of excess licensed product that meet all product release criteria. The storage facility may also distribute licensed product to the final user.

D. Facility Changes

1. Change in legal name of the applicant. This will cause the issuance of a new license number.
2. Relocation of a major facility where product manufacturing is performed and there is no change in SOP, equipment, and core center personnel, especially

center management and medical personnel. Report relocations of facilities that result in a change in core center personnel as a prior approval supplement.

a. Include relocation of all contractors where there is no change in SOP, equipment, and core personnel.
b. Do not include move of auxiliary facilities. These will be reported by submitting a revised Form FDA 2830 at the time of the move and by updating the applicant's organizational report in the annual report.

V. CHANGES UNDER 21 CFR 601.12(c)(5) - Changes requiring supplement submission prior to distribution of the product made using the change (30 days is waived). [CBE]

As described in 21 CFR 601.12(c)(5), in certain circumstances FDA may determine that, based on experience with a particular type of change, the supplement for such change is usually complete and provides the proper information. Likewise, there may be particular assurances that the proposed change has been appropriately submitted, such as when the change has been validated in accordance with a previously approved protocol. In these circumstances, FDA may determine that the product made using the change may be distributed under licensure at the time of receipt of the supplement by FDA. FDA recommends that the applicants have a mechanism to track the date FDA received the submission.

The applicant shall specify that the changes are being reported in this category by labeling the submission: "Supplement - Changes Being Effected." CBER will determine if the change has been reported in the proper category and will notify the applicant if it has not. Lack of notification does not constitute CBER approval of the changes reported in the supplement, merely that the changes were reported in the proper category. CBER review of the submission will proceed after it has been determined that the changes have been reported in the proper category. There may be instances where FDA determines, after the product made using the change has been distributed, that the information in the supplement fails to adequately demonstrate the continued safety or effectiveness of the product made using the change. In such cases, FDA will make all possible efforts to resolve problems with the applicant concerning the supplement submission. In cases where FDA determines that there may be a danger to public health due to the continued marketing of the product, or when FDA determines that the issues may not otherwise be resolved, the agency may require under this section that the applicant cease distribution of the product made using the change or that the product be removed from distribution pending resolution of the issues related to the change.

The following are changes that in FDA's experience could be implemented under 21 CFR 601.12(c)(5) at the time of receipt of the supplement by FDA without a previously approved comparability protocol:

A. Product Manufacturing/Procedural Changes

1. Use of another manufacturer's previously approved SOP, with written permission from the manufacturer.

B. Facility Changes

1. Voluntary revocation or permanent closure of a major facility. Closure of auxiliary facilities may be reported in the annual report.
2. Temporary move or closure of a major facility. The applicant should indicate the estimated time for the change and describe the plans for restarting operations at the original site in the submission.

VI. CHANGES UNDER 21 CFR 601.12(d) - Changes to be described in an annual report (minor changes). [AR]

Under 21 CFR 601.12(d), changes to the product, production process, quality controls, equipment, or facilities, that have minimal potential to have an adverse effect on the safety or effectiveness of the product are required to be documented in an annual report submitted within 60 days of the anniversary date of approval of the first product application in each year when the applicant has changes to report in this category. For changes under this category, the applicant is required to submit in the annual report a list of all licensed products involved, and a full description of the manufacturing and controls changes including: the manufacturing site(s) or area(s) involved, the date each change was made, and a cross-reference to relevant validation protocol(s) and/or approved SOP.

On October 20, 1997, CBER sent a letter to all licensed blood and plasma establishments notifying them of the date of their first product application approval. The month and day of this date represents the establishment's annual report date. Minor changes to any and all licensed products must be reported in the annual report within 60 days of this date. The applicant may submit a written request to CBER for an alternate date. CBER will notify the applicant if this date is acceptable. Once approved, this alternate date will become the new annual report date.

Annual reports should contain information about minor changes to any and all licensed products implemented since the prior annual report. Submit one original annual report and two copies to CBER for review.

CBER will review the annual report to determine if the changes were reported in the proper category. If the annual report contains changes that should have been reported as supplements, CBER will notify the applicant in writing and by telephone of those changes which should be submitted as supplements. In such cases, FDA will make all possible efforts to resolve problems with the applicant concerning the annual report. In cases where FDA determines that

there may be a danger to public health due to the continued marketing of the product, or when FDA determines that the issues may not otherwise be resolved, the agency may require under this section that the applicant cease distribution of the product made using the change or that the product be removed from distribution pending resolution of the issues related to the change. After the review, the annual report will be placed in the manufacturer's license file.

FDA considers the following types of changes to be minor changes that should be reported in an annual report:

A. Product Manufacturing/Procedural Changes

1. Implementation of a program to collect Source Plasma from normal donors with pre-existing disease associated, Red Blood Cell and/or HLA antibodies in Source Plasma (11).
2. Implementation of a FDA-approved AABB Uniform Donor History Questionnaire, if used without modifications or if modifications are more restrictive.
   ***NOTE:** SOP describing the uniform procedures should be submitted for review as PAS or CBE30 as noted previously in sections III.A.2. and IV.A.1.
3. Implementation of recommendations described in final FDA guidance documents, if followed without modifications and directed to be reported in this manner by the guidance document.
4. Change in quality control method if the procedure is consistent with the manufacturer's directions.
5. Addition of procedures or tests which are not required or recommended by FDA. (If the test or procedure is included in the informed consent, the form should not contain any exculpatory language or claims about the procedure or test.)
6. Change in collection sets or leukocyte reduction filters, if used according to manufacturer's instructions.

B. Equipment Changes

1. Changes or upgrades by the device manufacturer of automated apheresis equipment that does not affect the purity, potency or quality of the product(s), if the facility is already approved for the original procedure, e.g., upgrade in plasmapheresis equipment from Haemonetics PCS to Haemonetics PCS2 or from Haemonetics V-50 to Haemonetics PCS, MCS or MCS Plus.
2. Change in irradiation equipment used by the applicant or contractor, e.g., from gamma irradiator to linear accelerator or to a different gamma irradiator manufacturer.
3. Implementation of a blood establishment computer system to replace manual procedures. Report the name of the software manufacturer, name and version number of the software.
    a. Include the installation of commercially developed software or user (in-house) developed software.
    b. Include change in blood establishment computer software versions or manufacturers, provided that there are no major changes in the processes performed by the computer (e.g., adding an electronic crossmatch function) or no modifications by the user.
    c. Do not include initial requests for a variance to use a computer/electronic crossmatch. Requests for this type of change should be submitted under 21 CFR 640.120.
    d. Do not include data entry and retrieval database systems or any software that is developed and used only in-house.
4. Implementation of automated equipment to perform ABO/Rh, syphilis and infectious disease screening testing on donor blood samples.
5. Change in infectious disease screening testing methodology if the procedure is consistent with manufacturer's directions.
6. Change in equipment that performs total protein and serum/plasma protein electrophoresis on donor specimens.
7. Use of sterile connecting (docking) device to manipulate product in a sterile manner (e.g., take samples, attach transfer bag, needle, saline, anticoagulant or other processing solutions, prepare aliquots, pool products) if approved to manufacture the product and use of the device is consistent with manufacturer's directions.

C. Contractor Changes

1. Change in contract testing laboratory that performs reference or quality control testing. This does not include a change in contract testing laboratory that performs the infectious disease test of record that must be reported as a supplement.

2. Temporary use of a previously approved alternate or back-up contractor to perform a manufacturing step. Include the dates the alternate contractor was used. A permanent change in a contractor should be reported as a supplement.

D. Facility Changes

1. Addition or deletion of a self contained motorized vehicle used for blood and blood product collection.
2. Change in "doing business as" name that does not affect the legal entity name on the license.
3. Openings, moves and closures of auxiliary facilities. The manufacturer must send in a facility registration form (Form FDA 2830) within five days of an opening, move or closure of the center [21 CFR 607.21 and 607.26].

An annual report does not need to be submitted if the manufacturer does not have any of the types of changes listed above. However, CBER recommends that the manufacturer send a letter to CBER stating that no minor changes have been implemented during the reporting period. The letter will inform CBER that the manufacturer is not delinquent in submitting an annual report and therefore not subject to penalties stated in 21 CFR 601.12(g).

The following information should **not** be included in the annual report:

- Major or moderate changes that have received FDA approval as supplements during the reporting period, unless they are included in the organizational changes.
- Major or moderate changes submitted as supplements and currently under review by CBER.
- Shipment of source blood, plasma or serum that is repeatedly reactive for an infectious disease marker and is to be used in the manufacture of vaccines and licensed or unlicensed in-vitro diagnostic biological products. These shipments must still be reported in the manner stated in 21 CFR 610.40(d).
- Notification of the development of unexpected antibodies in donors participating in Red Blood Cell immunization programs. This information should be kept on file at the facility so that it may be reviewed during FDA inspections (7). If the development of unexpected antibodies is due to an error in immunization practices, it must be reported under 21 CFR 600.14.
- Error and accident or incident reports, fatalities and recalls. Manufacturers must still notify CBER, Office of Compliance and Biologics Quality, of these events using the current reporting requirements [21 CFR 600.12 and 600.80].
- Validation data compiled during the installation and qualification of new or upgraded equipment, computer systems or software. This information should be kept on file at the facility so that it may be reviewed during FDA inspections.
- Corporate changes which should be reported to FDA at the time the change occurs:
    - Change in corporate mailing address of the legal entity.

- Change in or addition of an authorized official.

Reporting Format for the Annual Report

The following is a recommended reporting format for the annual report. The manufacturer may choose to use a different format, but CBER requests that the report contain the information listed below. See appendices for examples of annual reports.

- Cover Letter – FDA encourages applicants to use a cover letter to introduce and summarize the submission.

- Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use (FDA Form 356h).
    1. Include U.S. license number of the manufacturer.
    2. Identify the time period covered in the report.

- Description of the current organizational practices.
    1. If organizational changes have occurred since the last report, submit a current organization chart with descriptive job titles.
    2. List the licensed products the manufacturer is currently approved to distribute in interstate commerce.
    3. List all the facilities where product manufacturing is performed, including the names of contractors performing a manufacturing step. Identify which manufacturing steps are performed by the contractor. Include the address and registration number of each facility.

- Full description of minor changes reported to approved applications.
    1. List products affected by each change.
    2. List the address of the facility or facilities where the change was implemented. Include the registration number of the facility.
    3. Include the date the change became effective.
    4. Reference any approved comparability protocols used to implement the change.
    5. Describe the SOP or process affected by the change.

VII. COMPARABILITY PROTOCOL UNDER 21 CFR 601.12(e)

The comparability protocol described in 21 CFR 601.12(e) is a supplement that establishes the tests to be done and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the safety or effectiveness of a product. The purpose of a comparability protocol is to allow for a more expedient distribution of product by permitting the applicant to submit a protocol for a change which, if approved, may justify a reduced reporting category for the particular change at the time the change is implemented. A new comparability protocol, or a change to an existing one, requires approval prior to implementation because it may result in decreased reporting requirements for the changes covered. The reporting category will be established at the time that the comparability protocol is approved.

If, during the implementation of an approved comparability protocol, the applicant must deviate from the protocol to resolve problems, deficiencies or discrepancies discovered during implementation, the change originally approved to be reported in a lower reporting category as a result of the comparability protocol should be reported in the higher category. The applicant should notify CBER as soon as possible to discuss the proper application procedure.

Types of changes for manufacturers of licensed blood and blood components intended for transfusion or for further manufacture that may be amenable to a comparability protocol filing include a change with a long planning or development cycle but a short implementation window or a change that will be repeated several times by the applicant in a similar, but not identical way. Examples of changes for which a comparability protocol might be useful are:

1. Acquisition of facilities operating under one manufacturer's license by another licensee.
2. Single change in the manufacture of a product that will be implemented in multiple facilities under a single license, e.g., plateletpheresis.
3. Change to use a cleared apheresis device for the collection of products approved for this device, e.g., use of Fenwal Amicus to also collect Platelets, Pheresis; Platelets, Pheresis, Leukocytes Reduced; and Fresh Frozen Plasma, concurrently with plateletpheresis.

FDA intends to publish additional guidance on the content and use of comparability protocols. In addition to the information usually submitted in a prior approval supplement, some or all of the following should be included in a comparability protocol.

1. Implementation plan
2. Validation protocol
3. Criteria for acceptance of product prepared under changed conditions
4. Training program

5. Quality assurance program, including quality control testing plan
6. Product submission sampling plan

VIII. LABELING CHANGES UNDER 21 CFR 601.12(f)

Under 21 CFR 601.12(f), changes to labeling are required to be submitted to CBER in one of the following ways: 1) As a supplement requiring FDA approval prior to distribution of a product with the labeling change [21 CFR 601.12(f)(1)]; 2) as a supplement requiring FDA approval but permitting distribution of a product bearing such change prior to FDA approval [21 CFR 601.12(f)(2)]; or 3) in an annual report [21 CFR 601.12(f)(3)]. Some examples of changes to labeling (product labels, circular of information, package inserts) that CBER currently considers to be appropriate for submission in each of the categories are listed below.* This list is not intended to be comprehensive. A completed Form FDA 2567 "Transmittal of Labels and Circulars Form" should accompany each submission to CBER.

***NOTE:** Changes in format only do not need to be reported. Report only changes in the content of the label. Product labels must be consistent with requirements stated in 21 CFR 606.121 for Whole Blood and blood components and in 21 CFR 640.70 for Source Plasma and should be consistent with recommendations in published guidance.

A. Labeling changes requiring approval prior to product distribution [21 CFR 601.12(f)(1)]: Where applicable, circular of information must also be submitted as part of the labeling submission.

1. Labels submitted as part of a pending application or Prior Approval Supplement.
2. Labeling which contains an additional claim. The applicant may need to provide documentation to support these claims.
3. Labels representing a change in the volume of Whole Blood collected, e.g., 450 mL. to 500 mL., with an approved SOP stating donor must weigh at least 110 lbs.
4. Labels representing the collection of Source Plasma to be manufactured into non-injectable products if already approved to prepare Source Plasma to be manufactured into injectable products. Labels representing the collection of Source Plasma to be manufactured into injectable products if already approved to prepare Source Plasma to be manufactured into non-injectable products.
5. Green base labels for units intended for autologous use only and labels printed using black ink for all text (exemptions to 21 CFR 606.121 approved as 21 CFR 640.120 variance).
6. Conversion from Codabar to ISBT128 labels.

B. Labeling changes requiring FDA approval but product may be distributed prior to FDA approval [21 CFR 601.12(f)(2)]:

1. Labels submitted as part of a Changes Being Effected (CBE30 or CBE) supplement.
2. Labels consistent with an FDA-approved uniform labeling guideline.
3. Print on-demand, black and white ABO/Rh labels.
4. Labels representing a change in FDA-approved additive/anticoagulant solutions used in blood product collection.

C. Labeling changes requiring submission in an annual report [21 CFR 601.12(f)(3)]:

1. Labels for Source Plasma collected from normal donors with pre-existing disease associated, Red Blood Cell and/or HLA antibodies.
2. Labels representing a change in "doing business as" name that does not affect the legal entity name on the license.

IX. FAILURE TO COMPLY UNDER 21 CFR 601.12(g)

In addition to other remedies available in the law and regulations, in the event of repeated failure of the manufacturer to comply with 21 CFR 601.12, FDA may require that the manufacturer submit a supplement for any proposed change and obtain approval of the supplement by FDA prior to distribution of the product made using the change.

X. REFERENCES

1. Federal Register, 7/24/97 (62 FR 39890), Final Rule: Changes to an Approved Application.

2. Federal Register, 7/24/97 (62 FR 39904), Guidance for Industry: Changes to an Approved Application: Biological Products, July 1997.

3. Federal Register, 10/29/97 (62 FR 56193), Workshop on the Biologics License Application (BLA) for Blood Products and Reporting Changes to an Approved Application, December 2, 1997. Sponsored by FDA, CBER.

4. Federal Register, 7/31/98 (63 FR 40858), Proposed Rule: Biological Products Regulated Under Section 351 of the Public Health Service Act; Implementation of Biological License; Elimination of Establishment License and Product License.

5. Federal Register, 5/10/99 (64 FR 25049), Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the Form FDA 356h "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use," May 1999.

6. Federal Register, 7/8/97 (62 FR 36558), Revised Form FDA 356h, Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use.

7. Workshop for Licensing Blood Establishments, January 30 & 31, 1995, Sponsored by FDA, CBER.

8. Federal Register, 5/14/96 (61 FR 24227), Final Rule: Elimination of Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products.

9. Federal Register, 10/15/97 (62 FR 53536), Final Rule: Revision of the Requirements for a Responsible Head for Biological Establishments.

10. Federal Register, 11/25/92 (57 FR 55544), Notice: FDA's Policy Statement Concerning Cooperative Manufacturing Arrangements for Licensed Biologics.

11. Draft Reviewer's Guide: "Disease Associated Antibody Collection Program," October 1, 1995.

12. Memorandum to All Licensed Manufacturers of Source Plasma: "Physician Substitutes," August 15, 1988.

APPENDIX A

Sample of a Blood Bank Annual Report

Annual Report for Community or Hospital Blood Bank
123 Sunshine Drive
Any town, USA xxxxx
U.S. License Number xxxx
Registration # xxxxxxx

Reporting period: January 1, 1998 to December 31, 1998

XYZ Blood Establishment is currently licensed to manufacture:

Whole Blood; Red Blood Cells; Platelets; Platelets, Pheresis; Fresh Frozen Plasma; Red Blood Cells, Irradiated; Platelets, Leukocytes Reduced; Source Plasma

See attached organizational chart, including a list of all facilities and contractors.

Equipment changes:

March 1, 1998

Removal of all Fenwal CS3000 and using Cobe Spectra exclusively for Platelets, Pheresis.

August 1, 1998

Implement use of computerized donor information system. LAN at all transfusion centers, Mainframe at Reg. No. xxxxxxx

Facility changes:

June 13, 1998

Closed Whole Blood Donor Center at 321 Sunshine Dr., Anytown, USA (Reg. No. xxxxxxx).

Procedure changes:

September 10,1998

Implemented Anti-HTLV-II testing in accordance with FDA guidance document (8/97). At the same time changed from Abbott HTLV-I EIA assay to Abbott HTLV-I/II EIA assay.

Contractual changes:

None

APPENDIX B

Sample of a Source Plasma Facility Annual Report

Annual report for Source Plasma Center
U.S. License Number xxxx

Reporting period: July 1, 1998 to June 30, 1999

XYZ Blood Establishment is currently approved to manufacture Source Plasma for further manufacture into injectable and non-injectable products collected from the following donors:

- Normal, non-immunized
- Pre-existing disease associated antibodies (CMV, RSV, HAV, VSV)
- Immunized with Red Blood Cells for the Rho (D) antigen

Minor changes:

Description of Change - Installed our 510k approved computerized donor information system in 3 of our facilities. We are using the same SOP and there have been no user modifications of the software. Staff training is on file at the facility.
Facilities using change - 123 Road, City1, State, Reg. No. xxxxxx1; 456 Street, City2, State, Reg. No.xxxxxx2; 789 Avenue, City3, State, Reg. No. xxxxxx3.
Implementation Date - Reg. No. xxxxxx1 - July 4, 1998; Reg. No. xxxxxx2 - September 7, 1998; Reg. No. xxxxxx3 - February 14, 1999

Description of Change - Started collecting plasma from donors with pre-existing disease associated antibodies to CMV, RSV, HAV and VSV.
Facilities using change - All
Implementation Date - August 31, 1998
Comments - SOP xx: Disease Associated Antibody Collection Program. We are using labels approved under label review number 19980810001.

Description of Change - Upgraded all of our Haemonetics PCS automated plasmapheresis machines to Haemonetics PCS-2. Documentation of staff training is on file at the centers.
Facilities using change - All
Implementation Date - December 10, 1998

See attached organizational chart.
See attached list of major facilities including contractors.

APPENDIX C

Sample of a Blood Establishment with Multiple Facilities

Annual Report for Blood Establishment with major and auxiliary facilities.
U.S. License Number xxxx

Reporting period: January 1, 1998 to December 31, 1998

XYZ Blood Establishment is currently licensed to manufacture:
Source Plasma, Whole Blood

Major Facilities: 123 Sunshine Drive
Any town, USA xxxxx
Registration # xxxxxxx

456 Snowstorm Street
Any town, USA xxxxx
Registration # xxxxxx1

Auxiliary Facilities: 321 Sunshine Drive
Anytown, USA
Registration #. xxxxxxx

See attached organizational chart.

Description of Change	Facilities using change	Implementation Date	Comments
Change in SOP • Revised SOP for training • Additional procedures for QC of electronic donor weight scale • Addition of procedures for handling audits and inspections	All	January 3, 1998 March 7, 1998 April 13, 1998	
Implement use of computerized donor information system	LAN at all centers, Mainframe at Reg. No. xxxxxx1	August 1, 1998	
Implemented Anti-HTLV-II in accordance with FDA guidance document (8/97)	All	September 10, 1998	All cellular products

Change in facilities and locations:
June 13, 1998 – Opened new Whole Blood donor center at 321 Sunshine Drive, Anytown, USA (Reg. No. xxxxxxx, if available) for the manual collection of Whole Blood only.

Change in major equipment: None
Change in donor suitability criteria: None, other than those already reported
Change in contractors: None

APPENDIX D

Table: Types of Facilities as Determined by the Manufacturing Steps They Perform

Facilities	**Major Facilities** (Major Facilities may perform some or all of the manufacturing steps listed below.)						**Auxiliary Facilities** (Auxiliary facilities only perform the steps listed below)		**Transfusion Services**
Manufacturing Steps	Collection Facility	Community Blood Bank	Component Preparation Facility	Hospital Blood Bank	Plasmapheresis Center	Product Testing Laboratory	Distribution Center	Donor Center	Hospital Transfusion Service
Manual WB collection	X	X		X				X	
WB component preparation		X	X	X					
Auto. Plateletpheresis	X	X	X	X					
Automated RBC apheresis	X	X	X	X					
Automated Plasmapheresis	X	X	X	X	X				
Manual Plasmapheresis	X	X	X	X	X				
Product testing		X		X	X	X			
Labeling	X	X	X	X	X				
Storage	X	X	X	X	X		X		
Distribute	X	X	X	X	X		X		
Irradiation		X	X	X					
Freeze/Deglycerolization		X	X	X					
Leukoreduction		X	X	X					
Compatibility testing		X		X					X

NOTES: WB = Whole Blood, Leukoreduction – does not include bedside filtration